REMARKS

The Office Communication mailed April 9, 2003, has been received and reviewed. Claims 1-9, 16-18 and 21-25 are pending and stand rejected.

The applicants thank the Examiner for the courtesy of the telephonic interview conducted July 30, 2003. As discussed in the interview, this response explains the applicant's position in regard to the terms "homologous" and "complementary," which distinguish the claims from Saiki *et al.*

Claims 1-9, 16-17 and 21-25 stand rejected under 35 U.S.C. § 103(a) over Saiki *et al.* (U.S. Patent 4,683,194) in view of Dattagupta (U.S. Patent 5,215,899). Claim 18 stands rejected over the same references in combination with Cronin *et al.*, therefore, this rejection is submitted to be improper for the same reasons as claims 1-9, 16-17 and 21-25.

Saiki *et al.* is alleged to disclose conducting a hybridization reaction using at least two homologous probes. Dattagupta is alleged to disclose the use of at least one probe is non-linear.

The applicants note that the Office has determined that Saiki *et al.* does not teach a non-linear probe (Office Communication of 4/9/03 at page 4). The applicants also submit that Saiki *et al.* does not disclose two homologous probes. Furthermore, the Office has acknowledged that Dattagupta does not disclose the use of at least two homologous probes. Thus, the claims are not obvious over Saiki *et al.* in view of Dattagupta, since neither reference teaches the use of at least two homologous probes.

In particular, Saiki *et al.* teaches one probe which is hybridized to a target sequence, subsequently, additional target sequence, having a mismatch located in the restriction site of the probe, is added to block the vast excess of probe sequence (*see* col. 3, lines 5-33). Thus, the blocking "oligomer is complementary to the probe" (col. 6, line 68 to col. 7, line 1). Non-linear probes, for example, molecular beacons, "are hybridization probes that can report the presence of complementary nucleic acid **targets** without having to separate probe–target hybrids from excess probes in hybridization assays" (*see* Tyagi *et al.* (2000), Wavelength-Shifting Molecular Beacons, *Nat. Biotech.* 18:1191-1196, 1191) (emphasis added). Tyagi *et al.* demonstrates that the complement of the probe is the target, and not a homologous probe, as required by the claims.

Thus, the blocking oligomer of Saiki *et al.* is not a second homologous probe.

Furthermore, the term "homologous" is defined in the specification, for example, paragraph 10 and Table 1, as two or more nucleic acid molecules having a significant degree of sequence identity. The claimed homologous probes are "complementary" to the target sequence, for example, *see* paragraph 9 of the specification, wherein specific pairing between complementary nucleotides in the probe and complementary target sequence can be established, *see* MOLECULAR BIOLOGY OF THE CELL p. 5 (Alberts *et al.* eds. 2nd ed, 1989). Thus, when one sequence is homologous to another sequence, the two sequences have a significant degree of sequence identity (for example, a G at the same position), which is distinguished from the complement where a G at a position requires a C at the corresponding position of the complement.

The complement has a dissimilar sequence, it is non-homologous. Thus, the blocking oligomer disclosed in Saiki *et al.* is complementary to the probe, not homologous to the probe. Therefore, Saiki *et al.* does not teach at least two homologous probes.

The Office also cites Example 1, claims 1-40 and column 5, lines 28-67 of Dattagupta as disclosing the use of at least two homologous probes and at least one of the homologous probes is non-linear (Office Communication of April 9, 2003, at p. 4). During the telephonic interview, the Examiner acknowledged that Dattagupta does not disclose at least two homologous probes. Therefore, Dattagupta is alleged to teach the use of at least one non-linear probe. The applicants submit that Dattagupta does not teach a non-linear probe. Rather, Datttagupta teaches a duplex region at the 3' end of a linear probe. Furthermore, Dattagupta does not teach the introduction of a mismatch to reduce background signals in a hybridization reaction.

Moreover, five years after Dattagupta and eleven years after Saiki *et al.*, Tyagi *et al.* (1998) stated that introducing "mismatches in non-linear probes resulted in very unstable hybrids" (specification at para. 6). Thus, the applicants assert that the Office has not established that it "would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the non-linear probe of Dattagupta in the method of detection ... of Saiki et al." as alleged by the Office (page 5 of the Communication), without

using impermissible hindsight obtained from the applicant's specification.

To establish a *prima facie* cases the prior art must provide some motivation to combine the references and there must be a reasonable expectation of success (MPEP §§ 2143, 2143.01 and 2143.02). "Both the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure." *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d (BNA) 1529, 1531 (Fed. Cir. 1988). The applicants submit that the Office has not established a motivation to combine the references or addressed the expectation of success.

Tyagi *et al.* demonstrates a teaching away, or a motivation **not** to combine the references, MPEP § 2145 (X)(D); Tyagi *et al.* (1998) Multicolor Molecular Beacons for Allele Discrimination, *Nature Biotech.* 16:49, 53, 52. Tyagi *et al.* teaches that mismatches in non-linear probes resulted in very unstable hybrids, thus, Tyagi *et al.* teaches away from the applicant's invention (even assuming for the sake of argument that Saiki *et al.* were to teach a mismatch in the probe, which it does not) (MPEP § 2143.01, citing *In re Young*, 927 F.2d 558, 18 USPQ2d 1089 (Fed. Cir. 1991) and *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)). Therefore, there is no motivation to combine the references. Further, the Office asserts that Dattagupta provides motivation to combine the references, since "the invention concerns methods for detecting ... a particular nucleic acid sequence with high sensitivity," (page 5 of the Office Communication). Detecting a sequence with high sensitivity does not address reducing the background of a hybridization reaction. Nor does it overcome the disclosure in Tyagi *et al.* that mismatches in a non-linear probe result in unstable hybrids or low hybridization affinity (Tyagi *et al.* at p.52; MPEP § 2143.01, citing *In re Young*). Thus, the applicants assert that the Office has not established a motivation to combine the references.

In addition, there must be a reasonable expectation of success (MPEP § 2143.02). Tyagi *et al.* teaches the person of ordinary skill in the art that a non-linear probe having a mismatich dissociates at a higher temperature, is more unstable, than a perfectly complementary probe-target hybrid (Tyagi *et al.* at p. 52). Therefore, one of ordinary skill in the art would not expect a mismatch in a non-linear probe to reduce hybridization background. To the contrary, one of ordinary skill in the art would have expected to have to lower the annealing temperature and

thereby increase background. Thus, Tyagi *et al.* predicts the failure of the claimed invention.

The applicants respectfully submit that, absent a motivation to combine and a reasonable expectation of success, the Office has not established a *prima facie* case under 35 U.S.C. § 103.

Therefore, Saiki *et al.* does not disclose a method, wherein at least two homologous probes are used. Further, Saiki *et al.* does not disclose a non-linear probe, as acknowledged by the Office (Office Communication of 4/9/03 at page 4). Moreover, Dattagupta does not disclose the use of at least two homologous probes, as acknowledged by the Office, and does not disclose a non-linear probe. Thus, neither reference discloses at least two homologous probes.

Moreover, the applicants submit that the Office has failed to demonstrate a motivation to combine the references. Therefore, the applicants submit that the claims are not obvious in view of the references.

Reconsideration and withdrawal of the rejection is respectfully requested.

Respectfully submitted,

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Tyagi *et al.* (2000), Wavelength-Shifting Molecular Beacons, *Nat. Biotech.* 18:1191-1196